Please replace the paragraph bridging page 17 and 18 with the following:

Linkage of a TM to one or more biological agents may be achieved by any means known to those in the art, such as genetic fusion, covalent chemical attachment, noncovalent attachment (*e.g.,* adsorption) or a combination of such means. Selection of a method for linking a TM to a biological agent will vary depending, in part, on the chemical nature of the agent and depending on whether the agent is to function at the basolateral surface, within the epithelial cell, or undergo transcytosis. Linkage by genetic fusion may be performed using standard recombinant DNA techniques to generate a nucleic acid molecule that encodes a single fusion peptide containing both the biological agent(s) and the TM. Optionally, the fusion peptide may contain one or more linker sequences and/or sequences for intracellular targeting (*e.g.,* KDEL (SEQ ID NO:44), protease cleavage sites, nuclear targeting sequences, etc.). The recombinant nucleic acid molecule is then introduced into an appropriate vector and expressed in suitable host cells. Techniques for generating such a recombinant molecule and expressing a fusion peptide are well known to those of ordinary skill in the art (*see, e.g.,* Sambrook et al., *Molecular Cloning: A Laboratory Manual,* 2d ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 1989). Any biological agent having a known polypeptide sequence may be linked to a TM by genetic fusion. For example, using recombinant techniques, one or more immunoglobulin-derived sequences (*e.g.,* single chain antigen binding proteins, hinge, Fv gamma or Fv kappa) may be linked to a TM at the N- and/or C-terminus.

Please replace the paragraph at page 20, lines 8-28 with the following:

These protease recognition sites are extremely useful in the design of scissile linkers enabling the delivery of drugs, imaging compounds, or other biological agents to the intracellular environment of epithelial cells or to the epithelial barrier in general. Delivery of such compounds to epithelial cells can be accomplished by using residues 585-600 of human pIgR (SEQ ID NO:45) or residues 601-630 (SEQ ID NO:111) as part of the scissile linker joining the biological compound to TM. Delivery of anti-cancer drugs to tumors of epithelial origin can be accomplished using a substrate recognition sequence of MMPs (SEQ ID NO:109) or residues 30-40 of procathepsin E (SEQ ID NO:39) as part of the scissile

linker to TM. Alternatively, scissile linkers may be designed from other cancer cell specific or epithelial barrier specific processing proteases which may be identified by the comparison of newly synthesized and secreted proteins or similar techniques. Other types of proteases that can be used to cleave scissile bonds can be found in the mammalian duodenum, for example. The enterokinase recognition sequence, $(Asp)_4$-lys (residues 3-7 of SEQ ID NO:26), can be used as a scissile linker for delivery of biological compounds to the duodenum by TM mediated transcytosis across the duodenum epithelial barrier. Proteolytic cleavage releases the biological agent with a small fragment of linker (*e.g.*, VQYT, SEQ ID NO:40, from procathepsin; EKVAD, SEQ ID NO:41, from pIgR; or IIGG, SEQ ID NO:110 from the general MMP substrate sequence). Such residual linker segments may in turn be further digested by proteolytic enzymes (*e.g.*, carboxypeptidase II or aminopeptidase I) to yield an unmodified biological agent.

Please replace the paragraph at page 27, lines 8-14 with the following:

Table 1 below provides some examples of representative combinations of TM (with or without immunoglobulin-derived sequence(s)) and biological agent(s). In some cases, linkers are also indicated. For such combinations, intracellular delivery may be achieved using appropriate scissile linkers. Alternatively, other intracellular targeting sequences (*e.g.*, KDEL (SEQ ID NO:44)) may be incorporated. In the absence of sequences that direct the TM intracellularly, the TMs provided in Table 1 deliver the biological agent(s) via transcytosis. Multiple orientations for all TM attachments are possible.

Please replace the paragraph bridging pages 44 and 45 with the following:

Assembly of D1.1 and insertion into the TM synthetic gene. A fragment of the TM DNA proximal to C2, called D1.1, encodes amino acids 9 to 20 of the TM. The DNA sequence and primary amino acid peptide sequence of D1.1 are shown in Table VI and SEQ ID NOS:10 and 20. D1.1 encodes the proximal amino acids of the TM Core polypeptide (residues 12 to 20) as well as a short peptide of three amino acids which serve to join the TM Core with a leader peptide (appropriate for the expression system employed for synthesis of TM). D1.1 is generated by annealing oligonucleotides 1.1 and 2.1 (SEQ ID

NOS:48 and 49 respectively) into a DNA duplex as described in Method 1. Oligonucleotides 1.1 and 2.1 have overhanging unpaired ends compatible with the unpaired ends of BamHI (or Bgl II) and Xba I, respectively. D1.1 is annealed into pTMC at the BamHI and Xba I restriction endonuclease sites of the multiple cloning region and the DNA fragments enzymatically ligated, in a manner similar to that described in Method 1 for pTMC, to form the vector pTMD1.1C.

Please replace table XI with the following:

TABLE XI

DNA and Primary Amino Acid Sequence of TpS2

101 102

cys ser asp asp asp asp lys ala gln thr glu thr cys thr val ala pro

gc gat gac gac gat aag gcc caa acg gag acc tgt act gtt gcg cct

act tcg cta ctg ctg cta ttc cgg gtt tgc ctc tgg aca tga caa cgc gga

arg glu arg gln asn cys gly phe pro gly val thr pro ser gln cys ala

cgt gaa cgg caa aac tgc gga ttc ccg gaa/gta aca ccc tct cag tgc gct

gca ctt gcc gtt ttg/acg cct aag ggc ctt cat tgt ggg aga gtc acg cga

asn lys gly cys cys phe asp asp thr val arg gly val pro trp cys phe

aat aaa ggc tgc tgt ttt gat gac acg gta cgg ggc gtt ccg tgg tgc ttc/

tta ttt ccg acg aca aaa cta ctg tgc cat gcc ccg/caa ggc acc acg aag

E5

wrd.

tyr pro asn thr ile asp val pro pro glu glu glu cys glu phe
(SEQ ID NO:26)

tac ccc aat aca att gac gtt ccg cct gaa gaa gag tgc gag ttt taa g
(SEQ ID NO:16)

atg ggg tta tgt taa ctg caa ggc gga ctt ctt ctc acg ctc aaa att cttaa
(SEQ ID NO:36)

Please replace the paragraph bridging pages 70 and 71 with the following:

Fluorescent compound targeted for retention in the endoplasmic reticulum.

The scissile peptide AIQDPRLFAEEKAVAD (SEQ ID NO:45) is prepared as described above to contain an amino terminal fluorescein and a free sulfhydryl from an additional cysteine at the carboxy terminal.- TM (100 nmol) purified from transgenic insect cells as described above is reacted with sulfosuccinimidyl 4-[N-maleimidomethyl]cyclohexane-1-carboxylate

E6

(sulfo-SMCC, 10 µmol, Pierce product #22322) and purified as described above. The purified TM-SMCC in ~1 ml buffer is immediately reacted with the fluoresceinated peptide containing a free sulfhydryl group (10 µmol dissolved in 200 µl DMF) as described above. The derivatized TM is then purified from the reaction mixture by column chromatography (NAP-10 column, Pharmacia). The ER retention signal KDEL (SEQ ID NO:44) is synthesized as part of the TM core protein by phosphoramidite oligonucleotide coupling as described above and ligated into an insect expression vector to create pTM. The final compound is referred to as TM(kdel)-peptide-FL.

Please replace the paragraph at page 7, lines 12-19 with the following:

Anti-cancer drug targeted for retention in the endoplasmic reticulum. The activated drug linker compound, prepared as described above, is coupled to the lysine residues of TM by adding a 20-fold excess of MRA-PLGIIGG (SEQ ID NO:109) and purified as described above. -The TM used in this preparation is isolated from transgenic insect cells. The ER retention signal KDEL (SEQ ID NO:44) is synthesized as part of the TM core gene by phosphoramidite oligonucleotide coupling as described above and ligated into an insect expression vector to create pTM. This conjugate is referred to as TM(KDEL)-MRA.

Please replace the paragraph bridging pages 72 and 73 with the following:

Intestinal trefoil factor attached to TM via a carbohydrate linker. The porcine intestinal trefoil factor (ITF) is purified using a specific antibody as described (Suemori et al., *Proc. Natl. Acad. Sci. USA 88*:11017-11021, 1991). TM, synthesized as described above by peptide coupling and corresponding to the structure described in Table II E. #2 is linked to the enterokinase recognition sequence, (Asp)4-Lys (residues 3-7 of SEQ ID NO:26), by procedures described above. The recognition sequence is synthesized from a Gly-thioester resin support yielding a C terminal Gly-αCOSH after cleavage. The sequence is further modified to contain an amino terminal cysteine. The released peptide is coupled to TM by reaction of the thioester and the bromoacetyl functional groups. ITF is then derivatized to be reactive with sulfhydryl groups by reaction with sulfo-SMCC as described above. After purification, ITF-SMCC is coupled to the (Asp)4-Lys-TM (residues 3-7 of SEQ ID NO:26) and purified as described above. The reaction results in coupling of ITF to TM via a peptide linker which is a substrate for enterokinase associated with the apical surface of the intestinal epithelial barrier. The compound is referred to as TM-ITF.

REMARKS

A new Sequence Listing paper copy and computer disk are filed herewith to correct informalities noted in the previously filed Sequence Listing. The specification has been amended herein to refer to the new sequence identification numbers provided in the Sequence Listing. The amendments to the specification add no new matter.